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Global FMD control—Is it an option?

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Abstract

The outbreaks of foot-and-mouth disease (FMD) in Europe in 2001 identified the vulnerability of the intensive agricultural industries in Europe and North America to the economic consequences of the introduction of a highly infectious animal disease. The very large illegal international trade in animal products bypasses the safeguards recommended by World Animal Health Organization (OIE) and put in place by governments to prevent the importation of foreign pathogens. If it is not possible to stop the entry of FMD virus, what are the options to mitigate the risk by reducing the area of the globe in which FMD is endemic? There are a number of constraints that would prevent global control of FMD; current vaccines are expensive, have a narrow antigenic spectrum, provide only short term immunity and are very fragile; diagnostics are also expensive, require training to use and if not handled properly lose sensitivity and specificity; we still do not understand the significance of carrier animals in the epidemiology of FMD, and whether it is necessary or possible to prevent the carrier state; and many decision support tools, such as models are currently more dangerous than useful in that they fail to fully accommodate all the complexities of the disease. The four national foreign animal disease laboratories in USA, Canada, UK and Australia together with the International Livestock Research Institute have put forward a proposal to address some of these constraints (the Global FMD Research Alliance, GFRA), not only to protect their own national livestock industries, but also to support FMD control programs in countries in which the disease is present.

Keywords: Foot-and-mouth disease; Global control; GFRA

1. Introduction

Foot-and-mouth disease (FMD) is an economically significant disease of cattle, sheep, goats and pigs, and cloven-hoofed wildlife species. It causes production losses, particularly to the dairy and pig industries and high mortality in young animals, and is a major constraint to international trade in live animals and their products. In addition to disruption of animal trade, FMD outbreaks have widespread economic and social impacts both in the short and long term, including disruptions of animal feed, veterinary pharmaceutical and tourism associated industries. The countries in which FMD is found reflects in many ways their level of economic development, being absent from Europe, North America and Australasia, sporadic in South America and endemic in most of Asia and Africa. The presence of FMD provides reason to restrict trade in animal products from affected countries to those without FMD, and thereby denies access by developing economies to the rich markets of the developed world, reducing incentives to improve productivity and efficiency. However, while FMD free countries enjoy the trading advantages that this status brings, their very reliance on maintaining this freedom leaves them very vulnerable should FMD virus be introduced [1]. In 1997 FMD virus caused widespread outbreaks in Taiwan, which

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resulted in the immediate closure of the export trade to Japan and South Korea and a loss of four billion dollars, 90% of which was lost export earnings. In 2001, the Netherlands slaughtered 200,000 animals vaccinated against FMD as part of the control programme during an outbreak that had spread from the UK, in order to re-establish the country's FMD trading position as quickly as possible [2]. Even without the loss of a significant export trade, the cost of the 2001 outbreak to the UK economy was over eight billion dollars [3].

Traditionally, the impetus to assist developing countries control production limiting diseases such as FMD was as part of a general aid package to alleviate poverty, improve nutrition and allow the establishment of an export trade that would further sustain the economy. But an additional incentive for FMD free countries to help infected countries control and possibly eradicate the disease is that it reduces the global level of circulating virus. Increased global trade and movement of people, both legal, and more importantly from a FMD perspective, illegal, provide opportunities for the virus to spread. Excepting the possibility of bio-terrorism, this spread is not intentional, and there are many examples of FMD spreading into previously free countries by illegal movement of infected animals or animal products as an accidental consequence of by-passing import regulations. The argument can thus be made that it is in the self-interest of FMD free countries to help control and eventually eliminate FMD from the globe, even if this exposes their own economies to the additional trade competition that would result.

There is the example of rinderpest where this approach has been successful. Rinderpest, the classic cattle plague, caused massive mortality of cattle in Europe and Asia and later in Africa, and was in part responsible for the establishment of the World Animal Health Organization (OIE). However, all strains of rinderpest virus are antigenically similar, so that a single vaccine can be used to protect against all field strains of the virus. The vaccine is a live virus vaccine which provides lifelong immunity following a single dose. Animals that have recovered from infection with rinderpest virus have a sterile immunity, with no live virus remaining as a persistent infection. Not only does persistent infection not occur, but also the virus survives very poorly outside the host, making mechanical transmission of the virus in animal products or on contaminated people or fomites not a feature of its transmission cycle. The host range of rinderpest virus is limited to cattle and other ruminants, with cattle being the predominant reservoir host. It was therefore possible to control and eradicate rinderpest by focussing on an internationally organized vaccination and surveillance campaign, similar to that which had successfully eradicated smallpox from the human population. But FMD is different from rinderpest. There are seven antigenically distinct serotypes of FMD virus, within which there are a wide spectrum of antigenically related but distinguishable strains. The vaccines against FMD are dead preparations of whole virus with adjuvant, which at best give 6 months protection against antigenically closely related field strains of the same serotype. The protection, which vaccines provide to ruminant species, is not sterile, and vaccinated animals may become infected. Infection may persist for a variable period of time after recovery from clinical disease or in vaccinated animals that have contacted live virus; in particular, the African buffalo can carry live virus for over 5 years and cattle for up to 3 years. FMD virus can also survive on clothes, boots, surgical instruments and vehicles and in milk from infected animals for sufficient time to be carried into contact with new susceptible individuals. The virus will also survive in infected meat from animals slaughtered during the viraemic stage of the disease. Thus, while it can be claimed that rinderpest eradication will likely become a reality in a few more years, the characteristics of the virus and the available control strategies predisposed to this success. In contrast, the diversity of FMD virus, its transmissability and the currently available diagnostics and vaccines make it highly improbable that the virus could ever be eliminated from the poorer countries of Africa or Asia.

In summary, it will not currently be possible to effectively control and eventually eradicate FMD from the world because of a combination of technical constraints, incomplete understanding of the epidemiology of the disease and lack of cost effective disease control strategies.

2. Vaccines

Currently, all FMD vaccines are produced by growing live virus in BHK-21 cells in roller bottles or in suspension under bio-secure conditions in large volumes. The virus is harvested, concentrated and inactivated, and mixed for use with a buffer and adjuvant, either oil or aluminium hydroxide and saponin. The potency of the vaccine is measured in PD50, such that a vaccine with a PD50 of six, when used at one-sixth the recommended dose will protect 50% of cattle inoculated with live virus, homologous to the vaccine virus, 21 days after single vaccination. The minimum potency for FMD vaccine should be three, but higher potency vaccine (containing more inactivated virus antigen per dose) is available for vaccine banks. Cattle are normally vaccinated twice, starting at an age when any maternally derived immunity will no longer interfere with the development of active immunity, and then every 4 or 6 months, depending on the likelihood that they will be exposed to infection. The use of vaccine in a naive population, such as would occur in a previously free country trying to control an introduction of virus will not be immediately effective. Following the first dose of vaccine, and depending on the potency of the vaccine, immunity will not develop for 4–5 days—higher potency vaccines induce earlier immunity [4] and are therefore recommended for vaccine banks for non vaccinating countries that retain the option to vaccinate to control an outbreak, such as European countries, Japan, USA, Canada, Mexico, Australia and New Zealand [5].

The choice of vaccine strain will depend on the country in which the vaccine will be used and the antigenic prop-

erties of the circulating field strains. The first decision is serotype, and then field strain characteristics. However, if veterinary surveillance is not adequately resourced, as is typical in many FMD endemic countries, the strains of FMD virus circulating in the region may not be known. This problem is compounded if inadequate import supervision allows the introduction of virus from neighbouring or sometimes distant trading partners. If endemic FMD co-exists with a productive dairy industry, such as found in the Arabian Peninsular, it may be necessary to include up to eight strains of FMD virus in the vaccine to protect against all the potential field strains.

But FMD vaccines will not prevent infection in cattle exposed to live virus, and may not prevent disease if the vaccine strain is antigenically different from the field virus or the exposure to live virus is very high. While many countries do bring FMD under control using vaccination every 6 months together with other zoo-sanitary control methods, where such additional control strategies are not applied, and the level of circulating virus is high, even vaccination every 10 weeks is not sufficient to stop clinical disease. FMD vaccines, because of their production methods, are expensive. For high yielding dairy cows or buffalo, the expense can be justified, but not for low producing subsistence animals, particularly if re-vaccination is required every 4 or 6 months. The vaccines also are very unstable outside the range of 2–8 °C, making their effective application in the tropics difficult. These factors together ensure that current vaccines will not be effective or consistently used in many of the poorer countries in which FMD is endemic.

3. Epidemiology of FMD

The seven serotypes of FMD virus produce a clinically identical disease in susceptible livestock. Some strains within each serotype appear more virulent than others, and some strains are shed in large quantities as aerosols from infected animals, giving them the opportunity, under favourable weather conditions, to spread considerable distances. However, the different serotypes also have subtly different epidemiological behaviours [6]. The three SAT serotypes, SAT1, SAT2 and SAT3, are generally restricted in distribution to Africa. Occasionally they are found in the Middle East, having spread with the movement of animals exported out of Africa, but they never persist. This is not because of effective intervention, as other serotypes in the Middle East, such as A, O and Asia1, thrive in spite of any control programme. Even within Africa, the SAT2 virus has a wider distribution and is more frequently found in cattle than the other two. All three are found routinely in the African buffalo. On the other hand, Asia1 virus is never found outside of Asia (except for a brief excursion into Greece in 2000). Type C is characterised by long disappearances from the circulating virus pool, the most recent of which gave optimism that it had completely died out from the globe. However, in 2003, it reappeared in central Brazil after a 10 years absence. There are many enigmas surrounding the behaviour of the different serotypes of FMD virus, most of which cannot yet be explained. The tendency by those unfamiliar with the virus is to assume that all strains and serotypes behave in the same fashion, which leads to significant errors of judgement.

Probably the most important of the questions concerning the epidemiology of FMD is the risk presented by the carrier animal. The carrier is defined as an animal from which live virus can be recovered after 28 days following infection [7]. This is not an exceptional situation, with over 50% of cattle exposed to FMD virus becoming carriers, irrespective of whether they were already ‘protected’ by vaccination. The establishment of the carrier state probably depends on the strain and serotype of FMD virus involved, and the duration of the carrier state depends on the species of ruminant affected and on the individual. While there is anecdotal and some strong field evidence that carrier cattle can cause new outbreaks of FMD, this has been impossible to show under controlled conditions. There are those that argue that the carrier state is not significant in the epidemiology of FMD, giving as example the successful eradication campaigns against FMD in South America—although the recent resurgence of FMD in Brazil and Argentina during 2005 and 2006 raises the question, how is the virus persisting in the region if not in carrier animals? The problem of the carrier animal is particularly important when considering the use of vaccination to control an outbreak, as vaccination does not prevent infection, and the diagnostic tools are not available to identify all vaccinated, carrier animals with 100% certainty. The guidelines which define trading conditions between countries of different FMD status published by OIE [8] provide evidence for the uncertainty surrounding the role that carriers might play in causing a new outbreak. FMD free countries that use vaccine to control an outbreak must wait 6 months before re-applying for disease free status, after showing evidence that the virus has been eliminated from the vaccinated animals; countries that do not use vaccine, or slaughter all the vaccinated animals immediately after the outbreak (as did the Netherlands in 2001), can apply for FMD free status after only 3 months. In 2001, the OIE Code required 12 months after the use of vaccine if the vaccinates were not slaughtered, and only after pressure from member countries following the European outbreak was this reduced to 6 months in 2002. Even the new EU legislation, which now more favourably considers the use of vaccine during an outbreak, rather than repeat the mass slaughter that occurred in the UK during 2001, specifies that vaccinated animals cannot be moved between EU countries after an outbreak [9].

The virus persists in the carrier animal in the basal layer cells of the pharyngeal epithelium, particularly those of the dorsal soft palate [10]. These animals have high levels of circulating neutralizing antibody, and the FMD virus is usually lytic to infected cells. How, therefore is it able to persist, and why would such a mechanism have developed if it were not

to the advantage of either the host or the virus, or both? The constant presence of virus may stimulate the production of cytokines in the host, which provide non specific resistance against other viruses that infect through the pharynx. The ability of the virus to survive for long periods in the carrier will allow it increased opportunity to infect new hosts. That we do not understand the mechanism of persistence and transmission should not be used as evidence that it is not important for the maintenance of FMD virus.

4. Diagnostics

If rapid and reliable penside diagnostics had been available during the 2001 UK FMD outbreak, fewer animals would have been slaughtered. Predictive model driven policies adopted to control the outbreak required the slaughter of infected animals within 24 h of detection, and all susceptible animals on contiguous (adjoining) premises within 48 h. Detection of infection was by clinical inspection, and as the majority of the animals involved in the outbreak were sheep, it was usually impossible to make a firm diagnosis because of the usually mild clinical signs of FMD in this species. There was not time within the 24 h to obtain laboratory confirmation and consequently large numbers of healthy animals were unnecessarily slaughtered [11].

A deficiency in the available diagnostics is the inability to reliably identify the persistently infected animal, in particular the vaccinated sheep or bovine that has had contact with live virus. The argument used to persuade the OIE that they could reduce the 12 months wait after vaccination to 6 months was based on confidence in the sensitivity of tests detecting antibodies to FMDV non structural proteins (NSP) that are elicited by infection with live, replicating virus. Animals that have been vaccinated with the dead virus vaccine produce antibodies to the structural proteins of the virus, but because the virus does not replicate, there is no expression of the non structural proteins, and therefore the animal does not produce antibodies to these proteins. Unfortunately, not all vaccinated animals, particularly those that have received high potency vaccine, will allow sufficient replication of virus for detectable antibodies to the non structural proteins to develop. This does not mean that they do not become carriers. As a herd test to show whether a vaccinated group of animals has been exposed to live virus, the NSP tests are probably close to 100% sensitive, but it cannot be used as an individual animal test. Conversely, some FMD vaccines, although inactivated do contain levels of non structural proteins sufficient to stimulate an antibody response, particularly after repeated vaccination, thereby producing false positive results. There is therefore, pressure on FMD vaccine manufacturers to purify their vaccines of non structural proteins. This is possible, but it further increases the cost of production [12]. An additional problem of NSP tests is that they do not distinguish between infected animals that have eliminated virus and those that are carriers.

5. Other control measures

The success of the rinderpest eradication campaign was not solely dependent on a good vaccine and adequate diagnostics. Surveillance for disease was an essential component, and following recognition of disease, the implementation of effective quarantine, disinfections and movement controls. As rinderpest does not spread except by the movement of infected animals, usually showing obvious signs of infection, the additional control measures ensured that outbreaks could be contained. Although FAO and OIE are now turning their attention to global FMD control through their Global Framework for Progressive Control of FMD and other Transboundary Animal Disease (GF-TADs) programme, there is little chance that they will be able to fully address and prevent the huge cross border movements of animals and their products that occurs in south east Asia and Africa, or the large illegal trade that occurs worldwide.

It is our opinion that there is little possibility that with currently available tools that FMD can be controlled on a global scale within a foreseeable timeframe.

6. The solution

There have been considerable advances made in vaccine technology, rapid and easy-to-use diagnostics, antiviral therapies, immunology, genomics, proteomics and disease control strategies driven by a variety of forces, including HIV, influenza, SARS and the aging populations of the developed world. The emphasis has been on human health issues, but the technology is equally applicable to animal health problems, such as the control of FMD. A limiting factor for this transfer of ideas is the few laboratories in the world able to work with live FMD virus, and while the European FMD outbreak of 2001 was a reminder to FMD free countries of the danger presented by the disease, much of the response has been inward looking, improving preparedness and tightening import controls. There was relatively little money targeted at generating a new paradigm in vaccine development, diagnostics or therapeutics, which would follow the lead set by the human disease control programmes.

This deficiency was recognized by the establishment of the Global FMD Research Alliance (GFRA), with the overarching goal to research, design, construct and develop a new generation of accessible and efficacious vaccines, diagnostics and antiviral agents for the management of FMD to the point of entry of the commercial registration process. The core of the GFRA is a consortium of research institutions; the Pirbright Laboratory at the Institute for Animal Health, UK; the joint US Department of Agriculture's and US Department of Homeland Security laboratory at Plum Island, New York, USA; the Australian Animal Health Laboratory at Geelong, Australia; the National Centre for Foreign Animal Disease, Winnipeg, Canada; and the International Livestock Research Institute (ILRI), Nairobi, Kenya.

The rationale being that by co-ordinating the research effort between these core laboratories and others that would be interested in joining the initiative, maximized use of available resources and expertise would be achieved, duplication of effort would be avoided, progress would be quicker, funding opportunities improved with major benefit from individual national investments realised by access to partner's state of the art laboratories and broad skill bases, and research results would be shared, resulting in the improved ability to respond to a FMD outbreak. The fundamental concept of the GFRA being that the alliance is set to achieve which no single research institution can accomplish in isolation.

National funding for each of the core partners inevitably has been directed at improved national preparedness for an FMD outbreak, and there was concern that requests for funding for the GFRA initiative would merely divert the existing funding each was already receiving. This led to the development of a dual programme, the first to develop improved tools with which to respond to the incursion of FMD virus into a free country, the second to apply these new tools to the control of FMD in endemic countries, taking into consideration the different economic conditions that generally prevail in infected regions. The intention is to seek new funding, from national governments recognizing the leverage in outputs that can be obtained from funding an international consortium working together and sharing results, and from overseas aid agencies working to improve nutrition and economic welfare in developing countries.

It is not the intention of this paper to explore all of the options available for improved vaccines, diagnostics, antiviral agents and disease control decision tools. Some of this work is already in progress, such as the use of an adenovirus vector vaccine expressing FMD virus genes [13], penside diagnostics, the use of portable PCR technology, vector expressed antiviral therapeutic cytokines [13], and more will follow. However, there are certain fundamental questions specific to FMD still not answered, such as the significance of the carrier state, and these will require more basic research on the immune response to infection, vaccine development and epidemiology. These are long-term projects that require funding commitment. It did not take long for the panic of the 2001 FMD outbreak to be replaced by concern for other emerging diseases, and a consequent re-direction of financial support. The intention of GFRA is to keep FMD on the agenda, and work towards solving the problems outlined above, before it re-appears in Europe, North America or Australasia.

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